Effects of the combination of candesartan and spironolactone on periostin and matrix metalloproteinase-1 and -2 expression in non-infarcted myocardium after myocardial infarction in a rat model of chronic heart failure

（書式１８）課程博士

学　位　論　文　要　約

博士論文題　Effects of the combination of candesartan and spironolactone on periostin and matrix metalloproteinase-1 and -2 expression in non-infarcted myocardium after myocardial infarction in a rat model of chronic heart failure(心筋梗塞後慢性心不全ラットにおける非梗塞部心筋のペリオスチン、マトリックスメタロプロテアーゼ１および２の発現に対するカンデサルタン及びスピロノラクトンの効果)

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[Introduction] Treatments for acute myocardial infarction (MI) have improved over the past three decades, markedly decreasing the mortality rate of MI during the acute phase. However, the incidence of heart failure post-MI remains high. The goal of this study was to elucidate the molecular and cellular mechanisms involved in the progression of cardiac remodeling and evaluate the effects of traditional treatment with angiotensin receptor blockers or aldosterone receptor antagonists. Collagen synthesis and degradation are important factors in cardiac remodeling. Recent studies have shown that periostin can directly interact with collagen type I and plays an important role in LV remodeling after MI by promoting collagen synthesis. And matrix metalloproteinases (MMPs) comprise a family of zinc-dependent proteases responsible for extracellular matrix degradation during cardiac remodeling under normal and pathological conditions. In the present study, I investigated the effects of an aldosterone receptor antagonist (spironolactone) and an ARB (candesartan) on cardiac remodeling and evaluated the expression of periostin, MMP-1 and -2 in the non-infarcted myocardium of rats during the progression of heart failure after MI.

[Methods] Eight-week-old male Wistar-Kyoto rats underwent either coronary ligation or sham operation. Rats in the sham-operated group were subjected to simulated surgery (SHAM group; n = 8). Echocardiography was performed 4 weeks after MI to rule out insignificant LV dysfunction, and MI rats were assigned to four groups (n = 6–8 each): MI group, spironolactone group (50 mg/kg/day), candesartan group (1 mg/kg/day), and combination group. Rats were treated for 8 weeks.

[Results] MI increased the expression of periostin and collagen types I and III in the non-infarcted myocardium; all treatments reduced the expression levels of these three proteins. Additionally, the elevated heart weights, decreased ejection fraction, and reduced fractional shortening were ameliorated by administration of candesartan alone or in

combination with spironolactone. Combined therapy had greater effects on the inhibition of periostin overexpression than the monotherapy. Moreover, spironolactone, but not candesartan, increased MMP-1 expression.

[Conclusions] In summary, periostin may modulate cardiac remodeling in rats with chronic heart failure after MI. Combined therapy with spironolactone and candesartan may be more beneficial than individual use of these drugs. The beneficial effects of spironolactone and candesartan may involve attenuation of periostin expression. MMP-1 may be related to the effect of spironolactone on cardiac fibrosis. These results reveal that periostin is a marker associated with disease progression and regression in chronic cardiac remodeling after MI and suggest that the measurement of periostin may be a sensitive tool for evaluating the severity, progression, and response to therapy in human CHF associated with MI.